Mortality Trends for Cervical Squamous and Adenocarcinoma in the United States

Relation to Incidence and Survival

Mark E. Sherman, M.D.
Sophia S. Wang, Ph.D.
Joseph Carreon, B.A., M.S.
Susan S. Devesa, Ph.D.

Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Rockville, Maryland.

BACKGROUND. In the United States, detection of squamous carcinoma in situ (CIS) by screening has led to reduced rates for invasive squamous carcinoma and lower mortality. Adenocarcinoma in situ (AIS) rates also have increased, but invasive cervical adenocarcinoma rates have not declined similarly. To make inferences about the effectiveness of screening, the authors assessed mortality trends for squamous and adenocarcinoma in relation to incidence of these tumors, incidence of their precursors and survival.

METHODS. Using data from the Surveillance, Epidemiology, and End Results program (SEER), the authors tabulated incidence per 10^5 woman-years for invasive carcinomas (1976–2000) and for CIS and AIS (1976–1995) by age (< 50 years, ≥ 50 years) and race (whites, blacks). Cumulative relative survival rates were tabulated for 1976–1995 and mortality rates were estimated for 1986–2000.

RESULTS. Among all groups, CIS rates approximately doubled whereas rates for invasive squamous carcinoma declined. Among younger whites, mortality declined from 1.12 to 0.93, and for older whites, mortality decreased from 5.02 to 3.82. Among younger blacks, mortality for squamous carcinoma decreased from 2.69 to 1.96. Among older blacks, the mortality rates declined from 14.88 to 9.15. Although AIS rates have increased dramatically among whites (all ages) and younger blacks, adenocarcinoma incidence and mortality rates have not changed greatly. Survival for patients did not change greatly within these age-race groups.

CONCLUSIONS. The authors concluded that increases in CIS seemed disproportionately large compared with improvements in mortality rates for squamous carcinoma. Despite increased reporting of AIS, declines in mortality for cervical adenocarcinoma have not been demonstrated conclusively. However, future analyses are required to evaluate these trends more completely. ***Cancer* 2005;103:1258–64.**
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The central purpose of cancer screening is to reduce mortality attributable to a targeted tumor within a population. Cervical squamous carcinoma presents an ideal screening opportunity because these tumors generally develop slowly through a multistage process.[1] Cytologic screening has proven remarkably effective in identifying women with squamous carcinoma in situ (CIS) and earlier precursors, which can be treated effectively before invasive squamous carcinomas develop.[2]

In contrast, the effectiveness of cytologic screening in reducing mortality from cervical adenocarcinoma remains unproven. The prevention of invasive cervical adenocarcinoma presents specific challenges: 1) the morphology of the earliest precursors (i.e., antecedents of adenocarcinoma in situ [AIS]) has not been defined; 2) AIS typically

Address for reprints: Mark E. Sherman, M.D., Division of Cancer Epidemiology and Genetics, National Cancer Institute, 6120 Executive Boulevard, Rockville, MD 20892-7374; Fax: (301) 402-0916; E-mail: shermanm@mail.nih.gov

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involves areas of the cervix that are difficult to sample (i.e., the endocervical canal); 3) invasive adenocarcinoma develops from small foci of AIS; and 4) historically, the diverse and sometimes subtle cytologic and colposcopic features of AIS have not been widely appreciated.[3–6]

Development of improved cervical sampling devices and methods of slide preparation, implementation of standards for assessing specimen adequacy, and dissemination of refined cytologic criteria undoubtedly have increased the sensitivity of cytologic testing and contributed to increasing rates of both CIS and AIS.[7–10] Predictably, increased rates of CIS have presaged later declines in rates of invasive squamous carcinoma. However, increasing rates of AIS have been associated with paradoxically stable or increasing rates of invasive adenocarcinoma, as previously reported in detail.[11–15] In addition, 2 findings are particularly concerning: 1) adenocarcinomas comprise a disproportionate percentage of tumors that occur among recently screened women (within 5 years),[16] and 2) a negative cytology report affords less protection against adenocarcinoma than squamous carcinoma.[17] These findings suggest that some AIS lesions may progress rapidly to invasion or fail to be detected by cytologic screening.

In contrast to incidence trends, mortality trends for cervical carcinoma stratified by histologic type have received relatively little attention. Although the numeric predominance of squamous carcinoma suggests that mortality rates for this histologic type would probably resemble those of cervical carcinoma as a whole, evaluation of mortality rates for adenocarcinoma, a relatively infrequent type, clearly requires a type-specific analysis. Analysis of mortality trends for invasive adenocarcinoma is important for assessing the performance of cytologic screening.

The rate of progression of AIS to invasive adenocarcinoma is unknown. However, it is reasonable to assume that some AIS lesions are incipiently invasive when detected, whereas others may have little tendency to progress for prolonged periods. Increased detection of incipiently invasive cases of AIS would probably reduce both the incidence and mortality rates for invasive adenocarcinoma within a few years. In contrast, detection of prevalent, more stable cases of AIS might have little, if any, immediate impact. Although rates of disease progression for individual cases of AIS are unpredictable, assessing mortality trends for invasive adenocarcinoma in the context of preceding incidence trends for AIS provides an informative context in which to assess cancer prevention efforts.

To make inferences about the effectiveness of cervical screening, we analyzed trends for cervical squamous and adenocarcinomas using data from the Surveillance, Epidemiology, and End Results program (SEER), a population-based group of registries administered by the National Cancer Institute (NCI).[18] Although incidence data for these cancers and their precursors have been reported, we have included these data to facilitate examination of national mortality trends in light of screening effects (reflected in rates of CIS and AIS), cancer prevention (reflected in rates of invasive carcinoma), and treatment effects (reflected in survival).

MATERIALS AND METHODS

Ascertainment of Cases

The current analysis included cases of cervical carcinoma reported to 9 SEER registries (Connecticut, metropolitan Atlanta, metropolitan Detroit, Iowa, New Mexico, Seattle Puget Sound, Utah, San Francisco-Oakland, and Hawaii), which record data for approximately 10% of the U.S. population.[18] Invasive incidence data were tabulated for the period 1976–2000 and in situ incidence (including cervical intraepithelial neoplasia 3 [CIN]3) data for 1976–1995 (SEER discontinued reporting for CIS and AIS in 1996). Survival data were tabulated for the period 1976–1995. Mortality data from the National Center for Health Statistics were analyzed for the years 1986–2000. Cases were categorized according to the International Classification of Diseases for Oncology as squamous carcinoma (8050–8130) or adenocarcinoma (8140–8490)[19] and then stratified by stage (in situ vs. invasive), as reported previously.[11] Other histologic types (including adenosquamous carcinoma) were not analyzed.

Analysis

The analysis focused on relating mortality trends to preceding incidence trends for invasive squamous and adenocarcinomas and their precursors (CIS and AIS). Using SEER*STAT software[20] (NCI, Bethesda, MD), we tabulated the incidence of in situ and invasive carcinomas per 100,000 woman-years by race (black or white) and age ($<$ 50 years or $\geq$ 50 years) for 5-year intervals: 1976–1980, 1981–1985, 1986–1990, and 1991–1995, and for 1996–2000 (invasive carcinomas only) in a manner similar to that recently reported.[11] Survival analyses for 1976–1995 were performed to assess whether improved survival for patients with cancer contributed substantially to changes in mortality. Specifically, cumulative relative survival, a measure of survival in the absence of competing causes, was estimated for 5 years of follow-up by comparing the survival of women with invasive cervical carcinoma with that of women without cancer, matched on time period, race, and age. Data for whites were stratified by age. Similar stratification for blacks was precluded by the smaller number of cases.

TABLE 1
Five-Year Survival for Cervical Squamous Carcinoma (1976–95)

Calendar period	Whites age < 50 yrs % ± 1.96 SE	Whites age ≥ 50 yrs % ± 1.96 SE	Blacks (all ages) % ± 1.96 SE
1976–80	80.4 ± 2.1	60.8 ± 2.5	64.1 ± 3.8
1981–85	79.2 ± 2.2	58.6 ± 2.9	61.1 ± 4.1
1986–90	80.2 ± 2.0	60.7 ± 3.1	59.2 ± 4.4
1991–95	81.0 ± 2.0	60.6 ± 3.2	60.3 ± 4.5

Cumulative relative survival expressed as percentage ± 1.96 standard error (SE).

TABLE 2
Five-Year Survival for Cervical Adenocarcinoma (1976–95)

Calendar period	Whites age < 50 yrs % ± 1.96 SE	Whites age ≥ 50 yrs % ± 1.96 SE	Blacks (all ages) % ± 1.96 SE
1976–80	82.5 ± 5.4	53.9 ± 7.1	45.7 ± 16.5
1981–85	86.4 ± 4.4	57.2 ± 7.7	54.8 ± 14.7
1986–90	85.5 ± 3.7	57.8 ± 7.0	57.2 ± 13.7
1991–95	88.0 ± 3.3	59.5 ± 6.9	52.8 ± 13.4

Cumulative relative survival expressed as percentage ± 1.96 standard error (SE).

U.S. mortality data for cervical carcinoma stratified by histopathologic type are not available. To estimate U.S. mortality rates separately for squamous and adenocarcinoma, we used a modification of the method described by Chu et al.[21] Briefly, we tabulated SEER incidence data for squamous and adenocarcinoma for three 15-year periods (1976–1990, 1981–1995, and 1986–2000), restricted to cases who died during three corresponding 5-year periods (1986–1990, 1991–1995, and 1996–2000). Each 15-year incidence period included the corresponding 5-year mortality period plus 10 previous years. The mortality rate for each 5-year period was estimated by multiplying the total cervical carcinoma mortality rate for the interval by the estimated percentages of the tumors that were classified as squamous or adenocarcinoma during the related 15-year incidence period. For example, to estimate mortality related to squamous carcinoma among white women < 50 years during 1991–1995, we used the SEER database to determine that there were 439 cases of incident cervical carcinomas diagnosed between 1981 and 1995 that were associated with cervical carcinoma deaths during 1991 to 1995. Of the 439 fatal cervical carcinomas, 306 (69.7%) had been diagnosed as squamous carcinomas. During 1991–1995, the total national mortality among whites < 50 years was 1.49 per 10^5 women-years. The product $1.49 \times 0.697 = 1.039$ is the estimated mortality among whites < 50 years during 1991–1995 that was attributable to squamous carcinoma.

Mortality rates were estimated for strata defined by race and age at diagnosis. All incidence and mortality rates were age-adjusted using the 2000 U.S. standard population within the broad age groups < 50 years and ≥ 50 years.

To facilitate observations concerning the relation of incidence trends to subsequent mortality trends for invasive carcinoma, we plotted the log of incidence for in situ and invasive carcinomas and mortality attributable to invasive tumors stratified by race, age, and calendar period. The calendar periods were plotted on the abscissa in 5-year increments with data shown at the mid-point for each period. Survival data were presented in table format.

RESULTS

Trends in Mortality from Cervical Squamous Carcinoma (1986–2000) in Relation to Incidence and Survival

Among younger whites, CIS rates increased sharply during the 1990s after only modest changes in preceding years, whereas rates of invasive squamous carcinoma declined 20% during 1976–2000 (Fig. 1). Among older whites, CIS rates have increased sharply since 1981–1985 and rates of invasive squamous carcinoma have decreased steadily.

Overall, 65% of deaths from squamous carcinomas among whites occurred among women ≥ 50 years. Among younger whites, mortality rates decreased 17.0% from 1.12 to 0.93 during 1986–2000. Among older whites, mortality rates decreased 24.0% from 5.02 to 3.82. Among whites, cumulative survival remained constant at approximately 80% for women < 50 years of age at diagnosis and 60% among older women (Table 1).

Among blacks in both age groups, CIS rates reached a nadir in 1986–1990, and then increased markedly in 1991–1995 (Fig. 1). Invasive squamous carcinoma rates declined steadily, declining 42% among younger blacks and 58% among older blacks.

Among blacks, 67% of deaths from squamous carcinomas occurred among women ≥ 50 years. During 1986–2000, mortality related to squamous carcinoma among younger blacks declined 27.1% from 2.69 to 1.96, whereas among older blacks a larger decline of 38.5% from 14.88 to 9.15 occurred during this period (Fig. 1). Survival among blacks (insufficient for age stratification) was similar to that of older whites and remained roughly constant over time (Table 1).

Trends in Mortality from Cervical Adenocarcinoma (1986–2000) in Relation to Incidence

For both younger and older whites, AIS rates increased multifold from 1976 to 1995 (Fig. 2) with higher absolute rates for women aged < 50 years. During this 20-year period, invasive adenocarcinoma rates in-

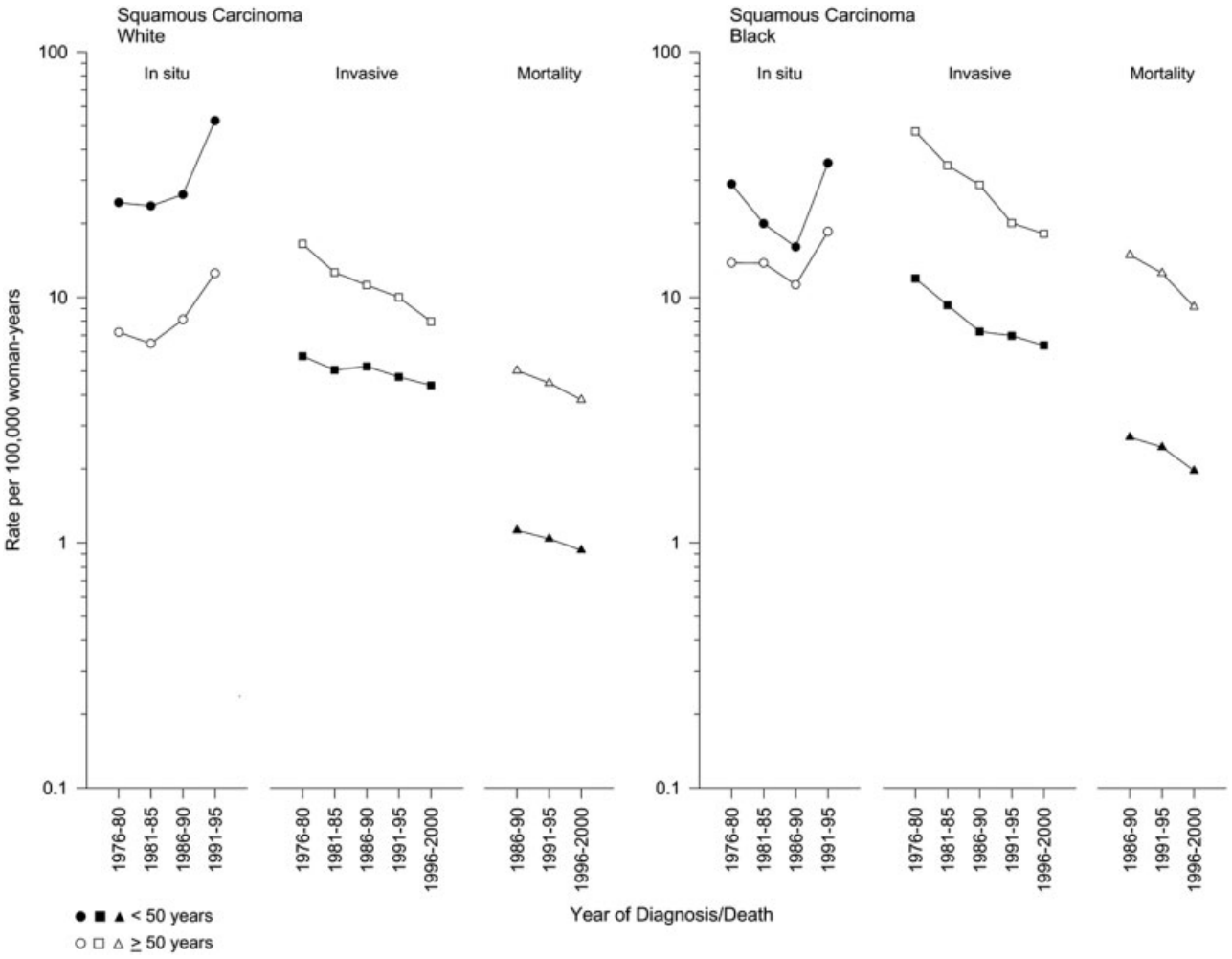

FIGURE 1. In situ and invasive incidence (nine Surveillance, Epidemiology, and End Results areas) and U.S. mortality trends by race and age: cervical squamous carcinoma.

creased 50% among younger whites compared with only 4% among older whites, and rates have continued to increase through 2000.

Among whites, 71% of deaths from adenocarcinoma occurred among older women. Among younger whites, mortality related to cervical adenocarcinoma fluctuated, increasing from 0.19 (1986–1990) to 0.26 (1991–1996), and then decreasing to 0.23 (1996–2000). Among older whites, mortality related to adenocarcinoma remained stable and consistently fivefold higher than among younger women (1986–2000). Survival among whites with adenocarcinoma increased slightly—from 82.5% to 88.0% for younger women and from 53.9% to 59.5% for older women (1976–1995, Table 2).

Among younger blacks, AIS rates more than tripled from1976 to 1995, whereas invasive adenocarcinoma rates fluctuated, with little overall change (Fig. 2). Before 1981, AIS was reported rarely among older blacks (not shown graphically). AIS rates seemed to have declined sharply in this group during 1991–1995 compared with previous years. Rates of invasive adenocarcinoma have fluctuated among older blacks, but have always been approximately fivefold greater than among younger blacks.

Among blacks, 80% of adenocarcinoma deaths occurred among older women. Mortality among younger blacks decreased steadily from 0.25 to 0.16 from 1986 to 2000, but this result was based on 24 total deaths. Mortality rates among older blacks increased 14.6% from 2.94 to 3.37 during 1986–2000. Survival among blacks (all ages) increased from 45.7% in 1976–1980 to 52.8% in 1991–1995 (Table 2).

DISCUSSION

Increased detection of CIS among both whites and blacks has been associated with substantial declines in

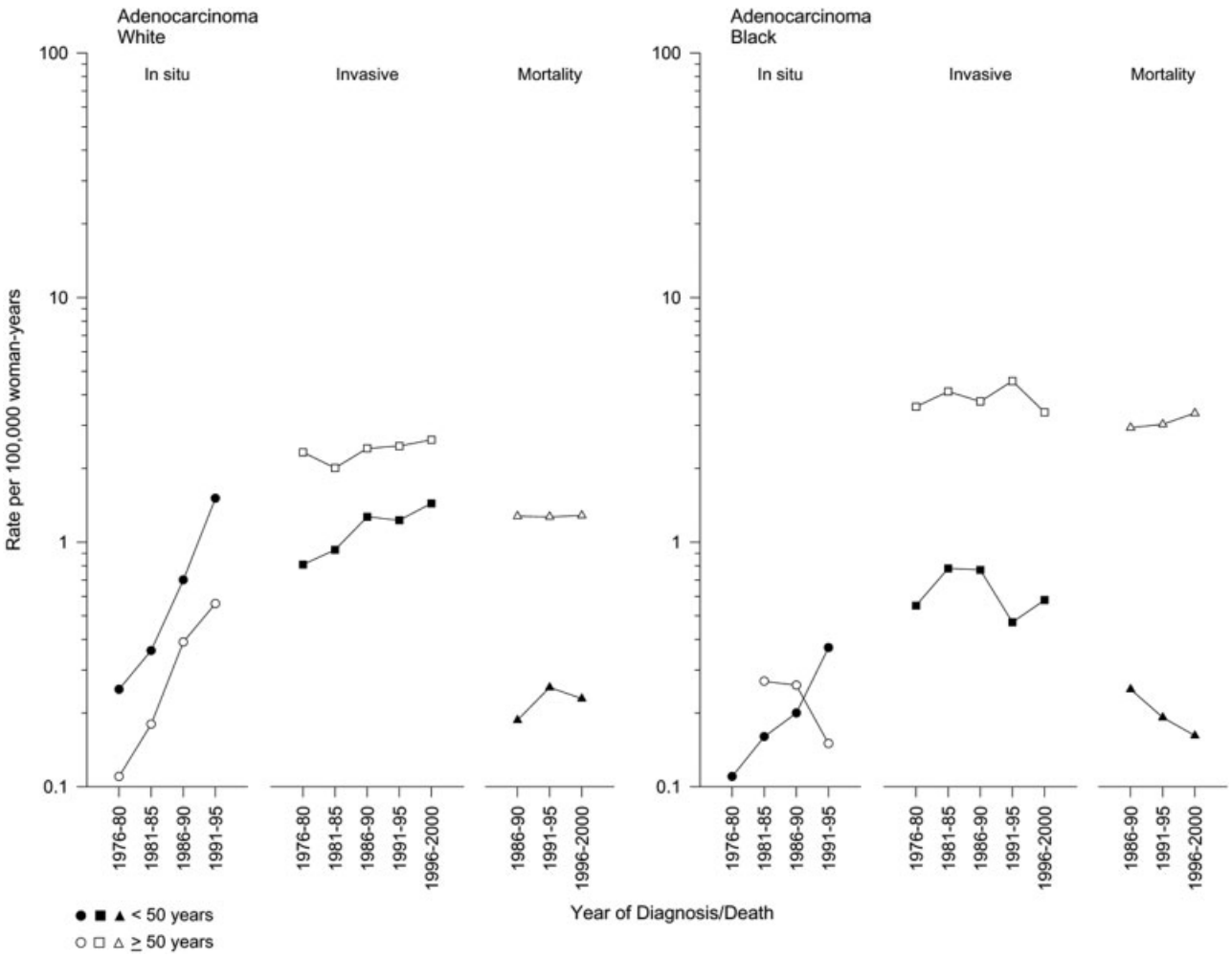

FIGURE 2. In situ and invasive incidence (nine Surveillance, Epidemiology, and End Results areas) and U.S. mortality trends by race and age: cervical adenocarcinoma.

rates of invasive squamous carcinoma and improved mortality. Survival among women with squamous carcinoma stratified by race and age has remained relatively constant, suggesting that any possible improvement in mortality is attributable to detection and treatment of cancer precursors, rather than improved treatment of invasive carcinoma. Consistent with this interpretation, a recent review found that chemotherapy treatments used to date have not been highly effective, although new combined modalities are promising.[22] The increased detection of CIS among the most frequently screened women (i.e., women aged $<$ 50 years) combined with the reduction in mortality among older women in subsequent time periods is also consistent with a screening effect. The observed increase in CIS incidence during the 1990s overlaps with the introduction of screening programs sponsored by the Centers for Disease Control and focused efforts to improve the performance of cytology.[23]

The recent reduction in mortality from squamous carcinoma seems modest, given the sharply increasing trends in CIS rates and the large increases in detection of less severe precursors. This observation suggests that some of the increased detection of CIS represents earlier detection without evident benefit, at least to date. Other data are consistent with this interpretation: 1) the mean age of women with CIS is nearly 20 years younger than that of women with invasive squamous carcinoma[24]; 2) CIN3 lesions that are not associated with invasion are much smaller than those associated with invasive carcinoma[25]; and 3) CIN2 lesions and frequently milder precursors are treated routinely in the United States, even though many of these lesions probably regress spontaneously.[26,27] Finally, Raffle et al.[28] estimated that 1000 women must

be screened for 35 years to prevent a single cervical cancer death and that 80% of high-grade dysplasias may not progress.

Compared with squamous carcinoma, screening for adenocarcinoma has been much less effective in reducing mortality, despite longstanding increases in AIS incidence rates among whites of all ages and younger blacks. Among whites, especially those < 50 years, increased detection of AIS has not been associated with sizable reductions in rates of invasive adenocarcinoma and mortality. The reasons for this observation are unclear. One possibility is that the cancer burden has increased in this group secondary to increased exposure to one or more etiologic factors.[29] If true, increased detection of AIS may have prevented a sharp increase in mortality. A second possibility is that the increasing rates of AIS may have been attributable mainly to diagnosis of prevalent lesions with little tendency to progress, whereas another set of AIS lesions that has been and remains less detectable by cytology accounts for many fatal cases of invasive adenocarcinoma. A third possible explanation might be that more effective detection of AIS is having a delayed benefit on mortality, which will become increasingly evident in future years. In this respect, it will be useful to determine whether possible declines in mortality related to adenocarcinoma among younger whites (1996–2000) and younger blacks (1986–2000) will continue. An analysis of recent data from an Australian screening program found that a negative cytologic result was associated with improved protection against adenocarcinoma compared with data from the same population in previous years. A history of a reportedly negative smear within 1 year or having had ≥ 1 smear with an endocervical component from 1994 to 2001 was associated with an approximately 3-fold reduction in risk of invasive adenocarcinoma.[30]

It is difficult to independently assess the effectiveness of screening for AIS and CIS. CIN (including CIN3/CIS) is frequently identified concurrently with AIS.[31] When CIN is not identified, it is possible, if not likely, that it was present earlier in the natural history of a human papillomavirus (HPV) infection but regressed before diagnosis. Data suggest that cytologic screening may be insensitive in detecting CIN lesions related to HPV-18[32] and that HPV-18 accounts for approximately 50% of adenocarcinomas compared with only 15% of squamous carcinomas.[2] If the endocervical canal represents a sanctuary site for persistent occult HPV-18 infections, failure to detect early manifestations of HPV-18 infection in squamous epithelium (e.g., koilocytoic atypia/CIN) could explain the strong association of this type with adenocarcinomas. Historically, and even currently, cytologic detection of CIN often leads to detection of cytologically unrecognized AIS. Studies to assess whether cytologic screening is less effective in preventing invasive adenocarcinomas related to HPV-18 compared with other types would be important, especially given the growing role of HPV testing as an adjunct to cytology in primary screening.

The interpretation of incidence and mortality trends for adenocarcinoma among blacks may differ from that among whites, but it is also limited by smaller numbers of cases. Additional data are needed to clarify these issues.

Although the absence of convincing declines in mortality related to cervical adenocarcinoma is troubling, cervical squamous carcinoma remains a much greater cause of cancer mortality. The considerably higher mortality associated with both histologic types of cervical carcinoma among older women is particularly relevant to discussions about setting an upper limit for routine cytologic screening. A recent study found that older age was related to reduced survival until age 75 years, and that among elderly women, general health and stage had a greater impact on survival than treatment efficacy.[33] These data underscore the probable importance of prevention strategies in older populations and the value of detecting and treating precursors of carcinoma among younger women. The role of HPV testing in determining the need for future screening among older women requires further study in light of evidence that a negative HPV test provides much longer protection against cervical neoplasia than cytology.[34] Primary prevention of adenocarcinoma through vaccination against HPV may prove particularly effective, given that the attributable fraction for HPV-16 and HPV-18 is higher relative to that for squamous carcinoma, which shows a greater diversity of HPV types.

Interpretation of the data presented in the current study is limited by changes in diagnostic practices and terminology and the lack of central pathology review. Findings for blacks are limited by small numbers. In addition, the length of follow-up may have been inadequate to demonstrate clearly the relations between increasing detection of precursors and anticipated declines in rates of invasive carcinomas and mortality. Future analyses with lengthier follow-up and consideration of ethnic diversity would be important. Our method for estimating mortality admittedly was limited by the follow-up data available through SEER. Finally, we can assume that nearly all cases of CIS and AIS were detected as a result of screening, but we do not know the screening history of the women in our dataset who were diagnosed with invasive carcinoma.

Despite these limitations, the failure of these data to demonstrate a substantial decline in mortality rates for cervical adenocarcinoma is of considerable importance. Future epidemiologic studies of cervical glandular lesions that include molecular testing for HPV and other factors might be useful in developing more effective cancer prevention strategies. Given the relative rarity of cervical adenocarcinoma, this will probably require a large study population.

REFERENCES

1. Schiffman M, Kjaer SK. Natural history of anogenital human papillomavirus infection and neoplasia. *J Natl Cancer Inst Mongr.* 2003;31:14–19.
2. Bosch FX, de Sanjose S. Human papillomavirus and cervical cancer—burden and assessment of causality [review]. *J Natl Cancer Inst Monogr.* 2003;31:3–13.
3. Krane JF, Granter SR, Trask CE, Hogan CL, Lee KR. Papanicolaou smear sensitivity for the detection of adenocarcinoma of the cervix: a study of 49 cases. *Cancer (Cancer Cytopathol).* 2001;95:8–15.
4. Lee KR, Minter LJ, Granter SR. Papanicolaou smear sensitivity for adenocarcinoma in situ of the cervix. A study of 34 cases. *Am J Clin Pathol.* 1997;107:30–35.
5. Schoolland M, Allpress S, Sterett GF. Adenocarcinoma of the cervix. Sensitivity of diagnosis by cervical smear and cytologic patterns and pitfalls in 24 cases. *Cancer (Cancer Cytopathol).* 2003;96:5–13.
6. Schoolland M, Segal A, Allpress S, Miranda A, Frost FA, Sterrett GF. Adenocarcinoma in situ of the cervix. Sensitivity of detection by cervical smear. *Cancer (Cancer Cytopathol).* 2003;96:330–337.
7. Nanda K, McCrory DC, Myers ER, et al. Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review. *Ann Intern Med.* 2000;132:810–819.
8. Sulik SM, Kroeger K, Schultz JK, Brown JL, Becker LA, Grant WD. Are fluid-based cytologies superior to the conventional Papanicolaou test? A systematic review. *J Fam Pract.* 2001; 50:1040–1046.
9. Solomon D, Davey D, Kurman R, et al. The Bethesda system 2001: terminology for reporting the results of cervical cytology. *JAMA.* 2002;287:2114–2119.
10. Solomon D, Nayer R. The Bethesda system for reporting cervical cytology. 2nd ed. New York: Springer, 2004.
11. Wang SS, Sherman ME, Hildesheim A, Lacey JV Jr., Devesa S. Cervical cancer incidence by race, subtype, and stage. *Cancer.* 2004;100:1035–1044.
12. Vizcaino AP, Moreno V, Bosch FX, Munoz N, Barros-Dios X, Parkin DM. International trends in the incidence of cervical cancer: I. adenocarcinoma and adenosquamous cell carcinomas. *Int J Cancer.* 1998;75:536–545.
13. Chan PG, Sung H-Y, Sawaya G. Changes in cervical cancer incidence after three decades of screening US women less than 30 years old. *Obstet Gynecol.* 2003;102:765–773
14. Smith HO, Tiffany MF, Qualls CR, Key CR. The rising incidence of adenocarcinoma relative to squamous cell carcinoma of the uterine cervix in the United States—a 24-year population-based study. *Gynecol Oncol.* 2000;78:97–105.
15. Zheng T, Holford TR, Ma Z, et al. The continuing increase in adenocarcinoma of the uterine cervix: a birth cohort phenomenon. *Int J Epidemiol.* 1996;25:252–258.
16. Hildesheim A, Hadjimichael O, Schwartz PE, et al. Risk factors for rapid-onset cervical cancer. *Am J Obstet Gynecol.* 1999;180:571–577.
17. Mitchell H, Medley G, Gordon I, Giles G. Cervical cytology reported as negative and risk of adenocarcinoma of the cervix: no strong evidence of benefit. *Br J Cancer.* 1995;71:894–897.
18. Ries LA, Eisner MP, Kosary CL, et al., editors. SEER cancer statistics review: 1973-2000. Bethesda: National Cancer Institute, 2003.
19. Percy C, Van Holten V, Muir C, editors. International classification of diseases for oncology. 2nd ed. Geneva: World Health Organization; 1990.
20. SEER*STAT. Available from URL: http://seer.cancer.gov/seerstat [accessed 2004].
21. Chu KC, Miller BA, Feuer EJ, Hankey BF. A method for partitioning cancer mortality trends by factors associated with diagnosis: an application to female breast cancer. *J Clin Epidemiol.* 1994;47:1451–1461.
22. Fiorica JV. The role of topotecan in the treatment of advanced cervical cancer. *Gynecol Oncol.* 2003;90:S16–S21.
23. Reynolds T. States begin DCD-sponsored breast and cervical cancer screening. *J Natl Cancer Inst.* 1992;84:7–9.
24. Plaxe SC, Saltzstein SL. Estimation of the duration of the preclinical phase of cervical adenocarcinoma suggests that there is ample opportunity for screening. *Gynecol Oncol.* 1999;75:55–61.
25. Sherman ME, Wang SS, Tarone R, Rich L, Schiffman M. Histopathologic extent of cervical intraepithelial neoplasia 3 lesions in the Atypical Squamous Cells of Undetermined Significance Low-grade Squamous Intraepithelial Lesion Triage Study: implications for subject safety and lead- time bias. *Cancer Epidemiol Biomarker Prevent.* 2003;12:372–379.
26. The ASCUS-LSIL Triage Study (ALTS) Group. A randomized clinical trial on the management of cytology of atypical squamous cells of undetermined significance. *Am J Obstet Gynecol.* 2003;188:1383–1392.
27. Nasiell K, Nasiell M, Vaclavinkova V. Behavior of moderate cervical dysplasia during long-term follow-up. *Obstet Gynecol.* 1983;61:609–614.
28. Raffle AE, Alden B, Quinn M, Babb PJ, Brett MT. Outcomes of screening to prevent cancer: analysis of cumulative incidence of cervical abnormality and modeling of cases and deaths prevented. *BMJ.* 2003;326:901–905.
29. Madeleine MM, Daling JR, Schwartz SM, et al. Human papillomavirus and long-term oral contraceptive use increase the risk of adenocarcinoma in situ of the cervix. *Cancer Epidemiol Biomarkers Prevent.* 2001;10:171–177.
30. Mitchell H, Hocking J, Saville M. Improvement in protection against adenocarcinoma of the cervix resulting from participation in cervical screening. *Cancer (Cancer Cytopathol).* 2003;99:336–341.
31. Ostor A, Rome R, Quinn M. Microinvasive adenocarcinoma of the cervix: a clinicopathologic study of 77 women. *Obstet Gynecol.* 1997;89:88–93.
32. Woodman CB, Collins S, Rollason TP, et al. Human papillomavirus type 18 and rapidly progressing cervical intraepithelial neoplasia. *Lancet.* 2003;361:40–43.
33. Brun J-L, Stoven-Camou D, Trouette R, Lopez M, Chene G, Hocke C. Survival and prognosis of women with invasive cervical cancer according to age. *Gynecol Oncol.* 2003;91:395–401.
34. Sherman ME, Lorincz AT, Scott DR, et al. Baseline cytology, human papillomavirus testing, and risk for cervical neoplasia: a 10-year cohort analysis. *J Natl Cancer Inst.* 2003; 95:46–52.